REMARKS

Reconsideration of the present Application is respectfully requested in view of the above Amendments and the following Remarks. Claims 55-77 are currently pending and under examination. By the present Amendment, new claims 78-85 have been added to more specifically recite certain embodiments and the presently claimed methods. No new matter has been added by these claims. Support for the new claims can be found in the specification as originally filed, for example, on page 8, lines 27-29, and in the claims. It should be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

Claim Objections

The Examiner objects to claim 70 as being a substantial duplicate of claim 56. Applicants respectfully request that this issue remains deferred until claim 56 is deemed allowable.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner rejects claims 55-77 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner asserts that the specification is non-enabling for methods of administering marrow stromal cells, wherein the stromal cells may either generate or repair blood vessels in a controlled manner at the desired site or treat a mammal having a disease, disorder or condition characterized by a blood vessel defect.

Applicants respectfully traverse the Examiner's grounds for rejection and submit that the specification is commensurate with the scope of the claims. Consistent with the purpose of the enablement requirement, the specification teaches a person skilled in the arts how to *make* and *use* the presently claimed subject matter without undue experimentation. Embodiments of the presently claimed subject matter are directed, in pertinent part, to methods for generating, regenerating, or repairing a blood vessel in a mammal, and methods of treating a disease, disorder or condition characterized by a defect in a blood vessel, the methods comprising

administering culture expanded autologous or allogeneic bone marrow stromal cells (MSCs) to the mammal, wherein the cells differentiate into cells of a blood vessel in said mammal.

The specification teaches a person skilled in the art by example how to *make* the claimed stromal cells using routine experimentation. For example, the specification provides exemplary guidance on isolating, enriching, and expanding MSCs as recited in the claims (*see, e.g.,* page 31, line 24 through page 32, line 10). A person skilled in the art can determine whether donor stromal cells are matched (*i.e.,* syngeneic, autologous, or allogeneic) according to routine techniques well-known in the art (*see, e.g.,* page 29, lines 15-18 of the specification).

The specification also teaches a person skilled by example how to *use* the stromal cells as claimed using routine experimentation. For instance, the specification teaches by example that MSCs may be administered to a mammal systemically, such as by intravenous injection, and provides exemplary dosages (*see, e.g.,* page 30, line 1 through page 33, line 4; and page 32, lines 15-17 and lines 25-27). Both Example 1 and Pereira *et al.* provide exemplary guidance in determining the fate of MSCs administered to a mammal, and in particular demonstrate how to determine whether MSCs properly differentiate and/or associate with the desired tissue (*see, e.g.,* page 31, line 7 through page 34, line 17; and Pereira *et al.*, *Proc. Natl. Acad. Sci. USA*, May 1995, Vol. 92, pp. 4857-4861, which is incorporated by reference into the instant application on page 36, lines 18-20). A person skilled in the art may also assess blood vessel generation (*e.g..,* angiogenesis) in a mammal using routine techniques known in the art, including, for example, computerized analysis of brightfield and epifluorescence images or digitized computed angiography (*see, e.g.,* Leunig *et al., Lab. Invest.,* 1994 Aug;71(2):300-7 and Schlaudraff *et al., Eur. J. Cardiothorac. Surg.* 1993;7(12):637-43). Following systemic administration, a person skilled in the art can therefore use the guidance as provided in the specification and the art to routinely demonstrate whether MSCs differentiate into a cell of a blood vessel, and thereby generate or repair a blood vessel as recited in the claims.

A person skilled in the art can also routinely diagnose and identify any mammal having any disease, disorder or condition that is characterized by a defect in a blood vessel, such as a well-known vascular disease. Once the mammal and disease are both identified according to known techniques in the art, a person skilled in the art can routinely treat the disease by administering MSCs to the mammal as discussed herein. Routine clinical parameters exist in the

art for monitoring these treatments, including flow measurements, pressure measurements, microcirculatory studies, and imaging (*see, e.g.,* LANZER, P. & ROSCH, J., VASCULAR DIAGNOSTICS: NONINVASIVE AND INVASIVE TECHNIQUES (Springer-Verlag 1994)). Applicants note that "a *considerable* amount of experimentation is permissible, if it is merely routine." *In re Wands,* 585 F.2d 731, 8 USPQ2d 1400 (Fed.Cir.1988). As noted herein, each of the steps necessary to *make* and *use* the claimed subject matter are routine to a person skilled in the art.

A person skilled in the art also understands from both the specification and the art at the time of filing that MSCs are capable of generating blood vessels as claimed. For instance, the present specification contradicts earlier reports indicating that MSCs did not have features characteristic of endothelial cells (*see, e.g.,* page 34, lines 5-10). Instead, the specification shows that cultured MSCs can serve as stem-cell-like precursors of mesenchymal tissues (*see, e.g.,* page 42, lines 16-19), which a person skilled in the art knows to include blood vessel tissues and the cells therein, such as endothelial cells. A person skilled in the art also knows that endothelial cells of the blood vessel are *central* to neovascularization, such as in angiogenesis.

By way of general explanation, the art at the time of filing describes that angiogenic growth factors may activate receptors present on endothelial cells in the vessel wall, after which the activated endothelial cells begin to release proteases that degrade the basement membrane in order to allow endothelial cells to escape from the original vessel walls. The endothelial cells then proliferate into the surrounding matrix and form solid sprouts connecting neighboring vessels. As sprouts extend toward the source of the angiogenic stimulus, endothelial cells migrate in tandem, using adhesion molecules. As other cell types migrate to the site of angiogenesis, these sprouts then complete the process by forming loops to become a full-fledged vessel lumen, thereby generating a blood vessel. This understanding in the art is contrary to the Examiner's assertion that the *contribution* of endothelial cells to vascularization is not synonymous with *generation* of blood vessels as claimed, merely because blood vessels are comprised of more than just endothelial cells, such as epithelial cells and smooth muscle cells (*see* the Action, page 4). Rather, as detailed herein, a person skilled in the art understands that the introduction of MSCs, which may differentiate to endothelial cells, may be synonymous with generating a blood vessel as claimed.

Applicants respectfully disagree with the Examiner if the rejection is based in part on the assertion that systemic administration of MSCs might inadvertently target undesired locations, wherein due to the plasticity of these cells subsequent differentiation could complicate, rather than treat a disease state (*see* the Action, page 4, citing Nagaya *et al.*; and page 5, citing Zisch *et al.*). Applicants submit that this basis for the Examiner's rejection is improper in multiple respects. For instance, the Examiner relies too heavily on post-filing references that arguably should not even be part of the record, and also fails to apply the appropriate legal standard to the claims.

The Examiner asserts that the rejection is based on the totality of art on the record (*see* the Action, page 6), but Applicants submit that this art of record is improperly and disproportionately applied to the claims. In general, the Examiner should not use post-filing date references to demonstrate that the patent is non-enabling, unless a person skilled in the art states that a particular invention is not possible years after the filing date. *See In re Wright*, 999 F.2d 1557, 1562, (Fed. Cir. 1993) and M.P.E.P § 2164.05(a). As previously made of record, however, the central teachings of these references support Applicants' position that it is possible to practice the presently claimed subject matter.

As previously made of record and as noted by the Examiner, Nagaya *et al.* show that MSCs are capable of engraftment in the myocardium and differentiation into both myocardiocytes and vascular endothelial cells (*see,* the Action, page 3), and state that the ability of MSCs to transform into endothelial cells supports the role they play in neovascularization or angiogenesis (*see* the Action, page 4). Nagaya *et al.* also demonstrate that the administration and migration of a relatively low number of MSCs to the target organ induces both angiogenesis and myogenesis, and improves clinical outcome (*see, e.g.,* Nagaya *et al.*, page H2676, first column). None of these statements or results could be remotely construed as a statement that it is not possible to practice the claimed subject matter.

On the balance, as also noted by the Examiner, the authors in Nagaya *et al.* make passing reference to a concern about the use of "mixed" cell populations. But the authors also explain that the cell surface markers of cultured cells were consistent with previous reports of MSCs (*see Id.*). Even assuming, *arguendo*, that the cells in Nagaya *et al.* were partially "mixed," these cells still demonstrate the capability to migrate, differentiate into vascular endothelial cells,

and improve clinical outcome. Moreover, there are no grounds to assert that the presently claimed MSCs are any more "mixed" than the cells reported in Nagaya *et al.*, despite the noted presence of a "few" adipocytes and macrophages. A person skilled in the art would not expect a few terminally differentiated cells such as adipocytes and macrophages to target undesired sites and differentiate into various different lineages, complicating disease treatment (*see* the Action, page 4). Nagaya *et al.* therefore contains nothing in either the results or the discussion that rationally equates to a statement that it is not possible to generate blood vessels or treat vascular diseases by administering marrow stromal cells as claimed.

The Examiner also relies on Zisch *et al.* and Dzau *et al.* for the premise that potential stem cell plasticity may cause transplantation at numerous cites, which may in turn cause "potential" undesired differentiation, altering the physiological state of the mammal (*see* the Action, page 5). Irrespective of the Examiner's selective focus on "potential pitfalls," Zisch *et al.* conclude that the "significance of adult EPCs as therapeutic vehicles for ischaemic tissue salvage has been validated" (*see, e.g.,* page 424). This assertion, and the underlying results outlined in each reference and previously made of record, hardly qualify as statements that practicing the presently claimed subject matter is not possible.

The Examiner's reliance on Yoon *et al.* is also problematic, as the potential concerns with heart calcification described in this reference are not likely relevant to methods of generating blood vessel cells in a mammal as presently claimed. For instance, as previously made of record, Yoon *et al.* directly inject whole bone marrow cells into the heart of rats, such that these hearts are directly and immediately populated with an arguably excessive number of foreign cells. In contrast, the presently claimed subject matter focuses on systemic administration, in which the various tissues are exposed to a relatively dilute population of stromal cells.

Also, as previously made of record, Yoon *et al.* use whole bone marrow, a heterogeneous, complex mixture of cells, including the stroma. In contrast, the instant claims recite the use of *enriched* MSCs. Regardless of this clear technical difference, the Examiner equates the enriched MSCs of the present claims with the potentially problematic, "heterogeneous mixture" of stroma cells as described in Yoon *et al.* (*see* the Action, page 6, citing page 3159, second column, of Yoon *et al.*). Applicants respectfully disagree with this

comparison. As noted by the Examiner, the cells of the instant claims are partially enriched for mesenchymal precursors, and contain a few macrophages and adipocytes (*see* the Action, page 6, citing page 32, lines 8-10 of the specification). The heterogeneous stroma as described in Yoon *et al.*, in contrast, is composed of multipotent progenitor cells, adipocytes, reticulocytes, endothelial cells, fibroblastic cells, and osteoblasts (*see, e.g.,* page 3156). The remainder of a "few macrophages and adipocytes" in the enriched MSC cultures as claimed does not provide sufficient basis to compare these marrow stromal cells to the "heterogeneous" stroma as described in Yoon *et al.* Rather, based on the differences between the cited reference and the presently claimed subject matter, a person skilled in the art is likely to conclude that administering enriched (*i.e.,* mostly homogenous) MSCs of the present claims will not lead to the problems described in Yoon *et al.*, such as heart calcification.

Mere mention of potential therapeutic concerns and routine hurdles in the field of stem cell transplantation, as emphasized by the Examiner in the cited references, is not equivalent to a statement that a particular invention is not possible. In reality, a person skilled in the art knows that potential therapeutic concerns exist in *all* fields of medical research (*i.e.,* most therapies in existence have potential negative side effects). Basic science authors *always* ring a note of caution, and almost invariably mention that most therapies *warrant further investigation* (*see* the Action, page 5). These peripheral statements are not relevant to the central teachings in the cited references, which validate that it is possible to practice the claims as recited. Since the cited post-filing references fail to state that practicing the subject matter of the instant claims is not possible, it is questionable whether the Examiner should rely at all on these references in rejecting the instant claims.

Applicants also submit that the Examiner is failing to apply the appropriate legal standard to the method of treatment claims. As noted in Applicant's Response dated May 22, 2007, even though a rejection under 35 U.S.C. §101 was never formally made of record, enablement rejections under 35 U.S.C. § 112, first paragraph, which are based on an alleged lack of disclosure relating to therapeutic efficacy, are analyzed under the same legal standard as a rejection under 35 U.S.C. § 101. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Applicants arguments of record are therefore directly on point, even though the Examiner has already determined that the claimed subject matter meets the requirements of 35 U.S.C. § 101. As with

§101, enablement rejections under § 112 are improper when based on alleged lack of evidence regarding human therapeutic implementation, as the Federal Circuit has emphatically rejected the position that human clinical testing is necessary. *See In re Brana*, 51 F.3d 1560.

The Examiner is also focusing disproportionately on the certainty of the ultimate therapeutic outcome in determining whether undue experimentation is required to practice the claimed subject matter. In fact, the courts have r ejected as too high the application of a "reasonable certainty" standard in determining the enablement of a disclosure. S*ee In re Angstadt,* 537 F.2d 498, 503 (CCPA 1976) (opining that if *Rainer*, as improperly relied on by the dissent, "stands for the proposition that the disclosure must provide guidance which will enable one skilled in the art to determine, w*ith reasonable certainty*, whether the claimed product will be obtained...then *all* 'experimentation' is 'undue,' since the term 'experimentation' implies that the success of the particular activity is *uncertain*"). Under this standard, a person skilled in the art is expected to live with a fair degree of uncertainty as to whether administration of MSCs will generate a blood vessel or ultimately treat a mammal with a disease, disorder or condition that is characterized by a defect in a blood vessel. As essential to the enablement requirement, however, the disclosure provides express guidance in how to routinely *make* and *use* the presently claimed subject matter without undue experimentation, as discussed herein. With this in mind, the cited post-filing references are used by the Examiner merely to speculate on the certainty of the therapeutic outcome (*i.e.,* the cells may "complicate, rather than treat a disease state") (*see* the Action, page 4), and to support an inappropriate standard for undue experimentation.

Applicants also disagree with the Examiner if the rejection is based in part on the assertion that the disclosure must provide empirical evidence supporting the full scope of the claims. As previously made of record, it is well established that neither examples nor reduction to practice are required for enablement. *See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (upholding the Board of Patent Appeals and Interferences enablement determination for claims directed to a poxvirus vaccine, when the disclosure contained neither examples nor reduction to practice of a poxvirus vaccine) (noting that "great expenditures of time and effort were ordinary in the field of vaccine preparation"). As in *Falko*, Applicants submit that great expenditures of time and effort are ordinary in the field of clinical stem cell

transplantation. Based on the guidance provided in the specification regarding routine experimentation protocols, the presence of working examples on how to isolate, enrich, culture and systemically administer the claimed MSCs, and the high level of skill in the clinical arts relating to diagnosing and monitoring vascular diseases, the present disclosure allows a person skilled in the arts to make and use the presently claimed subject matter without undue experimentation.

Nonetheless, without acquiescence to the grounds for any rejection and merely to clarify certain embodiments of Applicants' disclosed subject matter, new claims 78-85 have been added. Support for these claims can be found in the specification, for example, on page 8, lines 27-29; and in the claims. Embodiments of the new claims are directed, in pertinent part, to methods of generating a cell of a blood vessel in a mammal, the method comprising administering culture expanded autologous or allogeneic bone marrow stromal cells to said mammal, wherein said cells differentiate into cells of a blood vessel in said mammal, thereby generating the cell of a blood vessel. Applicants submit that these methods are fully enabled by the instant specification.

Applicants understand that the present Response is directed exclusively to an enablement rejection, but nonetheless submit for the Examiner's consideration the following remarks on the novelty of the new claims. Applicants note the arguments previously made of record in the Response dated November 30, 2006, which show that the subject matter of the new claims 78-85 satisfies the novelty requirements under 35 U.S.C. § 102(b) in view of the cited references of record. Neither Boisvert *et al.* (*J. Clin. Invest.*, 1995;96:1118-24) nor Caplan *et al.* (U.S. Pat. No. 5,197,985) describe each and every feature of the claim, as required under 35 U.S.C. § 102(b). Briefly, Boisvert *et al.* fail to describe administration of culture expanded marrow stromal cells, and Caplan *et al.* fail to teach differentiation of marrow stromal cells into cells of a blood vessel.

Moreover, a person skilled in the art would not consider as inherent the ability of MSCs to differentiate into cells of a blood vessel, as asserted by the Examiner in the Office Action dated May 31, 2006. As disclosed in the specification and discussed herein, earlier reports on MSCs indicated that the cells did not have features characteristic of such cells as endothelial cells (*see, e.g.,* page 34, lines 5-10). The instant specification demonstrates, to the

contrary, that cultured MSCs can serve as stem-cell-like precursors of mesenchymal tissues after systemic infusion (*see, e.g.,* page 34, lines 10-17), which a person skilled in the art understands to include cells of a blood vessel.

In view of the above amendments and remarks provided herein and previously made of record, Applicants submit that claims 55-85 satisfy the enablement requirements under 35 U.S.C. § 112, first paragraph, and respectfully request reconsideration and withdrawal of the enablement rejection.

Applicants respectfully submit that all the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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